CJNR 2012, Vol. 44 N° 3, 7–17

Discourse

The Gendered Ovary: Whole Body Effects of Oophorectomy

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Since oophorectomy in healthy women predates the commercialization of BRCA mutations screens, genomics cannot explain entirely why physicians and cancer specialists recommend this procedure for women at risk. Rather, one must situate the development of reproductive cancer genomics within a broader sociocultural context in which researchers bring to bear habits of mind about women, reproduction and motherhood. (Happe, 2006, p. 173)

Gendering Organs

The social world writes on all parts of the body, including, and perhaps most especially, the reproductive organs. Organs are not immune from the effects of gender. The depiction and attributes of organs, especially reproductive organs, reflect society's views on sexualities and the relative merits of being female or male (Laqueur, 1990; Martin, 1987). On the basis of this gendering, they can be assigned a positive or negative merit for a given body. For example, in some cultures the external portion of the clitoris is viewed as "male" and the foreskin of the penis as "female" — each must be removed in order to make a successful female or male body; the repercussions of that single act reverberate across the entire body (Einstein, 2008).

The ovaries, too, are gendered. Most of the medical discourse on the ovaries suggests that their only purpose is female reproduction. Internal and not easily accessed, they have become a site of fear and anxiety for the medical profession. In the United States alone, over 600,000 hysterectomies are done yearly, over half of which include bilateral salpingo-oophorectomy (BSO) to prevent *possible* future cancers, neoplasms, endometriosis, and pelvic pain (American College of Obstetricians and Gynecologists [ACOG], 2008). For women who have an increased risk

of ovarian cancer, the literature is replete with the instruction that "hysterectomy with bilateral salpingo-oophorectomy effectively reduces endometrial and ovarian cancer risk in women . . . and should be offered after completion of childbearing" (ACOG, 2008, p. 6).

While the biomedical literature includes acknowledgement of the well-known correlation between the loss of the ovaries and both cardiovascular disease and osteoporosis, these repercussions apparently do not outweigh the benefit of cancer risk reduction (ACOG, 2008). "Motherhood is, in fact, the only exception to the norm . . . I have yet to find a scientific report that acknowledges the acceptability of postponing, or avoiding altogether, oophorectomy because of health concerns" (Happe, 2006, p. 185). Furthermore, in one study a quarter of the women who were interviewed after BSO were not aware of the estrogen-production function of the ovaries at the time of the interview or before their operation (Gore, Hallowell, Jacobs, Mackay, & Richards, 2001). Those who were aware of this function understood it in terms of "femininity" and "being a woman" and not in terms of overall bodily health:

> You have your ovaries, and they are for producing eggs to make babies, and if they're wasted every month that's part of nature's cycle. And because they're there they give you all the hormones that you need and you are a woman. But some women, when they have hysterectomies have terrible sadness because they think, "oh well I'm not a full woman any more because I haven't got a uterus or a cervix or ovaries . . ." (Hallowell, 1998, p. 270)

This gendering of the ovaries has serious health ramifications in a reductionist biomedical view of the body. In such a view, the individual parts can be removed and/or altered without ramifications for the rest of the body. While there are cases for which the benefits of this perspective outweigh the risks, the risks must still be acknowledged and weighed. In the case of the ovaries, the gendering that has circumscribed their "use" has served to dampen what we also know well: The ovaries produce and secrete biochemicals (hormones) that affect every body system. Thus, their removal can lead to unintended health risks for any body system.

Considering the ovaries as only "female" reproductive organs is highly consequential for women who are counselled to have them removed for conditions such as chronic pain or cancer, or for prophylaxis in the case of the breast cancer gene mutations BRCA1/2m.

Women with BRCA1/2m are an especially important example of the problematic ramifications of gendering and reductionism, since most are healthy women who are *counselled* to have their ovaries and fallopian tubes removed (BSO) as prophylaxis for both breast and ovarian cancers (Narod, 2006). This reduces significantly their risk of breast cancer (Eisen

et al., 2005) and ovarian, fallopian, and peritoneal cancers (Finch et al., 2006) and is recommended prior to the age of natural menopause but *after childbearing*. Quality-of-life studies post-BSO reveal that women who elect it are relatively satisfied with their decision (Finch et al., 2011b). They report some difficulty with sexual functioning and vasomotor symptoms (Finch & Narod, 2011), but overall quality of life is reported to be similar before and after surgery (Finch et al., 2011a).

Such outcome studies that focus on patient satisfaction with the surgery overlook the fact that the human body is not made of organs that act independently of one another but, rather, is a cohesive, cooperative unit composed of interacting systems. Nowhere is this more important than in glands that secrete hormones, which are carried by the blood to every body system. With respect to the ovary, removing this source of 17-β-estradiol (one of three naturally occurring estrogens, E2) prior to age 50 has the potential to alter every body system. Unfortunately, this has been lost on us because we think of the ovaries as *reproductive organs*. This gendering of the ovaries, viewing them as necessary only for female reproduction, may have extremely negative effects on the rest of the body and have the unintended outcome of making women with BSO sicker.

Here, we use the occasion of BSO to briefly explore what is known about the effects of estrogen deprivation on five major areas of non-reproductive health and consider how all of these changes might act together to make a woman sick — despite allowing her to be free of breast and ovarian cancer.

Memory and Cognition

Recent epidemiological evidence suggests that women with oophorectomy prior to natural menopause have a significantly higher incidence of Alzheimer's dementia and Parkinson's dementia. The younger the woman is at the time of surgery, the greater the risk (Rocca et al., 2007). Additionally, women who lose both ovaries to surgery have a higher risk of developing dementia than those who lose only one ovary. Thus, BSO prior to the age of natural menopause is associated with a greater risk of developing neuropathologies. To date, studies comparing cognitive functions of women pre- and post-BSO all indicate a post-surgical deterioration of memory without estrogen replacement (Farrag, Khedr, Abdel-Aleem, & Rageh, 2002; Sherwin, 1988).

Osteoporosis/Osteopenia

A sampling of the literature suggests the importance of estrogens in bone development and maintenance. Estrogens and androgens inhibit osteoclasts (cells that break down bone) and promote the formation of

osteoblasts (bone precursors). Consequently, low levels of E2 are associated with lower bone density (Notelovitz, 2002). Not surprisingly, bone density in women who have had oophorectomy is lower than that of women in natural menopause (Pansini et al., 1995). Fractures in the wrist, vertebrae, and hips are increased moderately in women with BSO (Cummings & Melton, 2002). The younger a woman is at the time of BSO, the higher her risk of fracture (Melton, Crowson, Malkasian, & O'Fallon, 1996). Of women with BRCA1/2m and BSO, 26% had abnormal bone density, 57% had osteopenia, and 14% had osteoporosis (Chapman et al., 2011). However, a chart review of 226 patients revealed that none of the women on hormone replacement therapy (HRT) developed osteoporosis, suggesting that the negative bone outcomes are a result of estrogen deprivation (Cohen et al., 2012).

Cardiovascular Disease

BSO prior to natural menopause is a risk factor for cardiovascular disease (CVD), particularly coronary heart disease (CHD) (Lobo, 2007). Women who have BSO prior to natural menopause are 2.62 times more likely to develop CVD (Shuster, Gostout, Grossardt, & Rocca, 2008). BSO prior to 40 years of age is associated with elevated risk of ischemic heart disease compared to after age 45 (Lokkegaard et al., 2006). Women with BRCA1/2m and BSO had a serum total and LDL cholesterol concentrations significantly higher post-BSO than pre-, as well as significantly higher levels of lipids and homocysteine — all associated with increased risk of CHD (Verhoeven et al., 2009). Risk factors for CVD, such as metabolic syndrome (odds ratio = 2.46; Michelsen, Pripp, Tonstad, Trope, & Dorum, 2009) and salt sensitivity (Schulman et al., 2006), are all higher in women with BSO.

Immunocompetence

BSO has been associated with significant changes in immune-system cell activity. When healthy premenopausal women with total hysterectomy are compared with those who also had BSO, women with BSO have more serum cytokines interleukin (IL)1 and IL6 (Cantatore et al., 1995). Within 1 month post-surgery, women with BSO have some aspects of their immune systems activated, increasing into the second month of follow-up (Pacifici et al., 1991), while at the same time demonstrating immunodeficiencies (Kumru, Godekmerdan, & Yilmaz, 2004). Other immune-system cells, such as T lymphocytes, change their ability to cause invader cells to die; this change is correlated with a decrease in their estrogen receptors. Estrogen replacement increases the expression of these estrogen receptors (Zhang et al., 2009). E2 deprivation in general has

been associated with lowered immune reactivity (Gameiro, Romao, & Castelo-Branco, 2010). With ERT, levels of many components of the immune system have shown reversal (Kumru et al., 2004; Xia et al., 2009).

The risk of immune-system diseases and non-reproductive cancers may also increase. After BSO, risk of the autoimmune disease lupus rises (Costenbader, Feskanich, Stampfer, & Karlson, 2007), and women with BSO prior to age 50 have an increased risk of lung cancer (Parker et al., 2009). A chart review of women who received BSO due to BRCA1/2m revealed that most of those who had BSO prior to 55 developed a different type of cancer within a decade (excepting lung cancer, which developed at a later average age) (Cohen et al., 2012). BRCA1/2m itself is linked with lower immuno-competence even without BSO. Immune-system markers in women with BRCA1/2m are elevated, with significantly higher levels of serum cancer antigen mucin 1 (MUC1), whose overexpression and aberrant glycosylation is associated with adenocarcinomas (Hermsen et al., 2007). Similarly, healthy women with BRCA1m compared to age-matched controls have significantly decreased production of immune-system markers, with anti-tumour effects (Zielinski et al., 2003). Given that BSO may already impair the immune system, there may be a legitimate concern that those with BRCA1/2m undergoing prophylactic BSO are at greater risk of immunodeficiency.

Sleep

Sleep disturbances have long been associated with the physiological and psychological changes that accompany natural menopause. Thus, it is no surprise that sleep disturbances have also been associated with oophorectomy. In a study examining age and ethnic differences in self-reported sleeping problems of women at various stages of menopause, the prevalence of sleeping difficulties was highest in women who had undergone oophorectomy without HRT (Kravitz et al., 2003). Women who had undergone BSO before natural menopause had difficulty sleeping compared to the naturally menopausal controls (Benshushan et al., 2009). Compared to women who underwent hysterectomy alone, women with BSO for benign gynecological disease reported less improvement in sleep at 6 months post-surgery (Teplin et al., 2007). That it is estrogen deprivation that affects sleep quality is supported by studies in which estrogen is replaced. Healthy menopausal women with hysterectomies given HRT reported improved sleep quality (Polo-Kantola, Erkkola, Helenius, Irjala, & Polo, 1998). Estrogen replacement is also associated with an increase in both slow-wave and REM sleep (Antonijevic, Stalla, & Steiger, 2000), both of which are indicative of improved sleep quality. ERT was found

to improve sleep quality in naturally menopausal women compared to those not taking ERT (Moe, Larsen, Vitiello, & Prinz, 2001). The results of all of the studies cited above suggest that estrogen deprivation may affect sleep quality in women with BSO.

System Interactions

It is worth briefly considering the fact that changes in one of the above functions affect others. The immune and skeletal systems are interlinked in that the same factors (GM-CSF) that stimulate osteoclast recruitment and differentiation also increase activity of IL1 and IL6, cytokines that play a role in cartilage destruction in autoimmune diseases like rheumatoid arthritis (Cantatore et al., 1995). Also, after only 7 days post-surgery, premenopausal women who received hysterectomy with bilateral oophorectomy for benign reasons exhibited high levels of C-reactive protein (CRP), which were negatively correlated with levels of serum albumin, an inflammation marker (Kalyan, Hitchcock, Pudek, & Prior, 2011). Sustained elevated levels of CRP are associated with cardiovascular disease and metabolic syndrome (Kalyan et al., 2011), so this finding links heart health and the immune system in BSO. Estrogens may confer protection against various forms of vascular disease and their loss results in vulnerability to diseases such as atherosclerosis by inhibiting the production of inflammatory mediators (Ferreri, 2007). Further, changes in the immune system may affect the likelihood of women with BSO developing other cancers. Finally, long-term depression and anxiety post-BSO (Rocca et al., 2008) may be associated with troubled sleep and insomnia (Motivala, Sarfatti, Olmos, & Irwin, 2005).

Conclusion

Here, we have raised the possibility that the reductionism inherent in biomedicine and the gendering of the ovaries for female reproduction affects the types of treatment that are acceptable for prophylaxis or cure. We have used the example of removal of the ovaries prior to natural menopause, and in order to broaden the discussion beyond women's childbearing capabilities we have addressed bodily functions not linked directly with reproduction. Due to the ubiquitous effects of estrogens, the ramifications of early estrogen deprivation potentially affect the whole body. Sadly, gender has focused us narrowly on women's reproductive capacities, leaving us short-sighted with respect to all the other effects. Once we acknowledged that there are widespread effects of ovary removal, we would need to carry out clinical trials of estrogen replacement in all of these health domains, bearing in mind the differences in the type of estrogen being administered and the regimen of administra-

tion. Perhaps we would also need to encourage the development of estrogen analogues (SERMS) that will not act on the breast or the ovaries but will act on the rest of the body. As well, technologies that allow for successful imaging of the ovaries would need to be developed so there could be successful "watchful waiting" for women.

Methods for reducing the risk of breast and ovarian cancer are important; while removal of the ovaries does reduce this risk, it is detrimental from the perspective of every other body system. There are wide-ranging physiological changes in women with BSO, and health practitioners and patients need to be aware of these when considering the costs and benefits of BSO — especially women with BRCA1/2 mutations. The ovaries are not just for reproduction. Let us de-gender them for the health of the entire body.

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Acknowledgements

We thank Mei Huang and Aftab Mirzaei for their contributions to the research for this article.

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